A Unique 3-Chlorobutenolide Annulation Sequence

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Spiro 3,3-dichlorooxetane-2-ones rearrange under Lewis acid catalysis, accompanied by loss of HCl, to afford fused 3-chlorobutenolides in high yield.

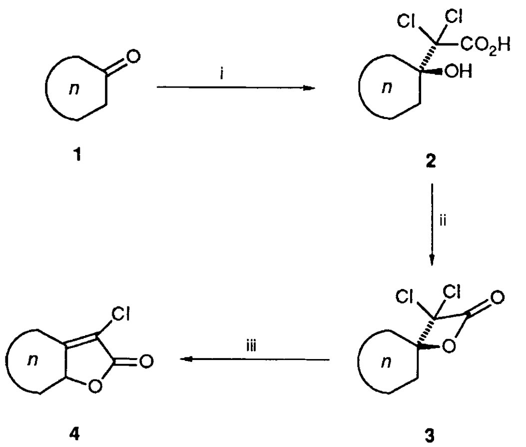
Unsaturated lactones, fused to a carbocyclic ring, are common in biologically active natural products, consequently a number of synthetic strategies have been recorded.[1] In almost all cases, fused butenolides are prepared *via* oxidation of the corresponding saturated lactones; this typically adds at least two steps to the sequence. We wish to report a novel sequence that enables the annulation of a 3-chlorobutenolide functionality to a cycloalkanone in only three steps. Chlorobutenolides are particularly attractive moieties since they serve not only as facile Michael acceptors,[2] but can be easily converted to alkyl or unsubstituted butenolides *via* metallation.[3]

The key reaction in this sequence, shown in Scheme 1, entails the ring expansion of spiro 3,3-dichlorooxetane-2-ones (β-lactones) with the concommitant elimination of hydrogen chloride to afford a butenolide. Although spiro β-lactones are accessible in a single step *via* the cycloaddition of dichloroketane to cycloalkanones,[4] our experience with difficult work-up and low yields for this transformation led us to examine other approaches. After significant experimentation, we developed a very serviceable method that involves the synthesis of dichloro β-hydroxy acids[5] followed by dehydration to the β-lactones. As indicated in Table 1, the yields are quite high for all ring sizes examined.

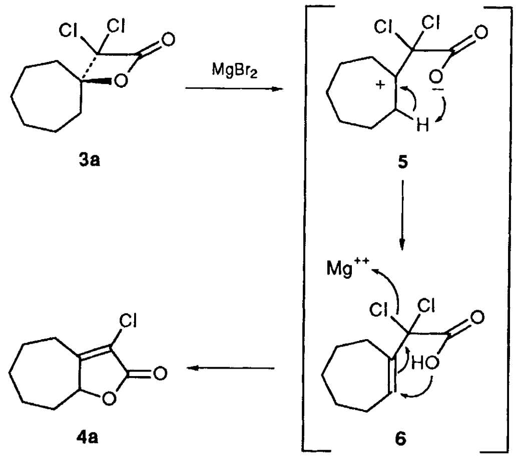
The specifics are illustrated for the preparation of fused butenolide **4e**. Cyclopentadecanone **1e** was added to a solution of dilithiodichloroacetate (from dichloroacetic acid and two equivalents of lithium diisopropylamide) in tetrahydrofuran–hexamethylphosphoramide at −84 °C (liquid nitrogen–ethyl

Table 1

Compounds	*n*	Yield of **4** (%)	$\nu_{C=O}$ /cm^{-1}
a	7	71	1775.1
b	8	73	1770.0
c	10	75	1771.1
d	12	83	1774.0
e	15	92	1774.7



Scheme 1 *Reagents and conditions*: i, Cl_2CLiCO_2Li; ii, $PhSO_2Cl$, pyridine; iii, $MgBr_2$, Et_2O



Scheme 2

acetate bath) and quenched at −84 °C† to afford the β-hydroxy acid **2e**, which was converted without purification‡ to the β-lactone **3e** upon treatment with benzenesulphonyl chloride in pyridine at 0 °C.[6] After purification *via* bulb-to-bulb distillation, **3e** was treated with freshly prepared anhydrous magnesium bromide etherate§ in ether for 8 h to afford the fused 3-chlorobutenolide **4e** in 92% yield.

A reasonable mechanism for this intriguing transformation is formation of the 2,2-dichloro 3-alkenoic acid *via* an E_I-type process, followed by a metal-assisted S_N2' cyclization (Scheme 2).[7] This aspect is currently being examined experimentally.¶

The operational simplicity and brevity of this sequence should provide an attractive alternative to the currently available synthetic methods for the synthesis of fused butenolides. We are actively pursuing extensions of this method to other butenolides bearing a variety of α substituents.

We wish to thank the donors of the Petroleum Research Fund, administered by the ACS, along with the Research Corporation, for support of this research. The 300 MHz NMR spectrometer was acquired with the assistance of the National Science Foundation (CHE-8815619).

Received, 4th September 1990; Com. 0/04015K

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6 For experimental details, see T. H. Black, W. J. DuBay and P. S. Tully, *J. Org. Chem.*, 1988, **53**, 5922. These compounds exhibited IR spectra in accordance with dichloro β-lactones ($\nu_{C=O}$ *ca.* 1860 cm^{-1}).

7 For a related reaction, see A. Roedig, B. Heinrich, W. Krieger and M. Schlosser, *Liebigs Ann. Chem.*, 1970, **733**, 105.

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† This is critical to avoid the formation of the epoxy acid.

‡ Attempts to purify these materials, *via* chromatography or distillation, invariably resulted in decomposition. IR spectroscopy was employed to establish the presence of a carboxylic acid function ($\nu_{C=O}$ *ca.* 1705 cm^{-1}).

§ Prepared *via* the reaction of magnesium with 1,2-dibromoethane.

¶ In experiments involving pentan-3-one as the starting material, small amounts of the corresponding 3,3-dichloro (saturated) butyrolactone were isolated. This material, when treated under the rearrangement reaction conditions for three days, was recovered quantitatively and unchanged. The intermediacy of dichlorobutyrolactones is therefore unliklely.